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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,048	01/26/2006	Philipp Hadwiger	A2038-7052US	3878

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EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
03/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/543,048	HADWIGER ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86,94-98,100-102 and 110-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86,94-98,100-102 and 110-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/19/2008 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 12/19/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/21/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. With entry of the amendment filed on 07/22/2008, claims 86, 94-98, 100-102, and 110-119 are pending in the application. Applicant has canceled claims 1-85, 87-93, 99 and 103-109.

Response to Applicant's arguments in the remarks filed 12/19/2008 is moot because the previous rejection of record has been withdrawn.

New Claim Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 86, 100-102, and 110-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. et al. (US 2003/0139363), Fosnaugh et al. (US 2003/0143732), Frecht et al. (US Patent No. 7,097,856) and Florence et al. (Journal of Controlled Release, 2000, Vol. 65: 253-259 of record 08/22/2007)

The instant claims are drawn to a dsRNA comprising a complementary RNA strand and a sense strand and only one lipophilic group having a logKow exceeding 1, 1.5, 2 or 3, wherein the lipophilic group is covalently attached to the 5' end of the complementary strand or the 5' end of the sense strand, wherein the dsRNA is complementary to a (+) strand RNA virus, wherein the linkages between the 5' comprises a phosphodiester group, wherein the linkage does not comprise a phosphodiester group, wherein the lipophilic group is a sterol, cholesteryl or selected from the group as listed in claim 98, wherein the dsRNA has overhangs on one or both ends, wherein the dsRNA is between 16 to 30 nucleotides in length, wherein the target gene is expressed in cells as listed in claim 117 and wherein the dsRNA targets HCV.

Kay et al. et al. teach dsRNA that efficiently inhibit viral gene expression and targeting hepatocyte cells using a dsRNA molecule is capable of inhibiting the expression of a Hepatitis C Virus (see pages 13-15). Kay et al. et al. do not teach dsRNA comprising conjugates at the 5' end of the antisense strand, do not teach a conjugate such as a lipophilic group which has a logKow i.e. an octagonal/water partition coefficient exceeding 1 and do not specifically teach the lipophilic group is linked at the 5' end with a phosphodiester group.

Fosnaugh et al. teach double-stranded RNA molecules comprising a sense and an antisense strand wherein the antisense strand is complementary to a target gene. The dsRNA taught by Fosnaugh et al. can comprise sense and antisense strands that are from 19 to 25 nucleotides in length and can further comprise nucleotide overhang regions at the 3' or 5' end (see at least pages 3-5). Fosnaugh et al. teach the dsRNA comprises a conjugate covalently attached to the dsRNA wherein the conjugate is attached at the 5' end of either strand (see paragraph 0068) and teach the conjugate can be linked with biodegradable linkers as well as phosphodiester linkages (see paragraphs 0172-0173). Fosnaugh et al. teach the conjugate molecule can be any ligand that can mediate cellular uptake of the dsRNA wherein the modifications increase the stability of the molecule and enhance the cellular uptake of the molecule which is important for *in vivo* applications (see paragraph 0032).

Frecht et al. teach making lipophilic groups such as dendrimers that are useful as delivery vehicles for nucleic acids and dendrimers are well known in the art (see columns 1 and 2). Frecht et al. teach the dendrimers are efficient delivery vehicles for

therapeutic agents and have low toxicity (see column 2). Frecht et al. teach the nucleic acids can be double-stranded RNA and teach methods of conjugation of the dendrimer to the nucleic acid and teach the dendrimers can be attached using linkers (see columns 31-33, for example).

Florence et al. teach a lipophilic dendrimers are efficient drug delivery vehicle for molecules because the dendrimer is small and can translocate across the cell layer (see page 254). Florence et al. teach such dendrimers has an octagonal/water partition coefficient of 17.5 (see page 255).

It would have been obvious to one of skill in the art to conjugate a lipophilic group, as taught by Frecht et al., to the 5' end of a dsRNA taught by Kay et al. et al. It would have further been obvious to attach the dendrimer using linkers such as taught by Frecht et al. and Fosnaugh et al.

One of skill in the art would have wanted to incorporate a lipophilic group such as a dendrimer taught by Frecht et al. onto the dsRNA to mediate cellular uptake of the dsRNA more efficiently in methods of targeting HCV as taught by Kay et al. et al. Because Fosnaugh et al. teach conjugates are effective delivery agents and teach conjugates can be attached to a dsRNA at the 5' end of either strand; it would have been a design choice and a matter of routine experimentation to covalently attach the dendrimer to the 5' end of the complementary strand using any of the linkers as described above. Moreover, one would have wanted to use a dendrimer given that Florence et al. teach dendrimers are of the optimal size that can be delivered to cells

and can be efficiently used as a delivery vehicle to deliver molecules across the cell layer which increases the molecules bioavailability.

One would have expected success at conjugating the dendrimer taught by Frecht et al. and Florence et al. to dsRNA given each teach methods of synthesis of dendrimers, Frecht et al. teach methods of conjugation to nucleic acids.

Thus, the instantly claimed invention would have been obvious to one of skill in the art at the time the invention was made.

Claims 86, 94-98 and 110-119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kay et al. et al. (US 2003/0139363), Fosnaugh et al. (US 2003/0143732), Manoharan, M. (20030064492, "Manoharan I") and Cook et al. (U.S. Patent No. 6,803,198) and evidenced by Manoharan, M. (Applicant's IDS 02/13/2006, "Manoharan II").

The instant claims are drawn to a dsRNA comprising a complementary RNA strand and a sense strand and only one lipophilic group, wherein the lipophilic group is covalently attached to the 5' end of the complementary strand or the 5' end of the sense strand, wherein the dsRNA is complementary to a (+) strand RNA virus, wherein the linkages between the 5' comprises a phosphodiester group, wherein the linkage does not comprise a phosphodiester group, wherein the lipophilic group is a sterol, cholesteryl or selected from the group as listed in claim 98, wherein the dsRNA has overhangs on one or both ends, wherein the dsRNA is between 16 to 30 nucleotides in

length, wherein the target gene is expressed in cells as listed in claim 117 and wherein the dsRNA targets HCV.

Kay et al. et al. teach dsRNA that efficiently inhibit viral gene expression and targeting hepatocyte cells using a dsRNA molecule is capable of inhibiting the expression of a Hepatitis C Virus (see pages 13-15). Kay et al. et al. do not teach dsRNA comprising conjugates at the 5' end of the antisense strand and do not specifically teach the lipophilic group is a sterol, or carbamate linked cholesteryl or wherein said group is linked at the 5' end with or without a phosphodiester group.

Fosnaugh et al. teach double-stranded RNA molecules comprising a sense and an antisense strand wherein the antisense strand is complementary to a target gene. The dsRNA taught by Fosnaugh et al. can comprise sense and antisense strands that are from 19 to 25 nucleotides in length and can further comprise nucleotide overhang regions at the 3' or 5' end (see at least pages 3-5). Fosnaugh et al. teach the dsRNA comprises a conjugate covalently attached to the dsRNA wherein the conjugate is linked at the 5' end of either strand (see paragraph 0068) and teach the conjugate can be linked with biodegradable linkers as well as phosphodiester linkages (see paragraphs 0172-0173). Fosnaugh et al. teach the conjugate molecule can be any ligand that can mediate cellular uptake of the dsRNA wherein the modifications increase the stability of the molecule and enhance the cellular uptake of the molecule which is important for *in vivo* applications (see paragraph 0032).

Manoharan I teach methods of increasing the stability of an inhibitory nucleic acid and teach conjugation of lipophilic groups enhances the cellular uptake of such

molecules. Manoharan I teach such groups can be fatty acids, sterols, cholesterol and aromatic groups (see paragraph 0018-0019). Manoharan I teach such conjugates can be attached using linkers as described in paragraph 0039.

Cook et al. similarly teach methods of increasing the stability of an inhibitory nucleic acid and teach attaching a carbamate cholesterol group increases the stability of said molecules (see columns 5 and 6).

It would have been obvious to one of skill in the art to use a known oligonucleotide conjugate, such as a sterol or aromatic group or a cholesteryl carbamate, as taught by Manoharan et al. and Cook et al., to link to a dsRNA at the 5' end as taught by Kay et al. et al. and Fosnaugh et al.

Such oligonucleotide conjugates taught by Manoharan et al. and Cook et al. were known in the art at the time of filing of the instant application to efficiently conjugate to inhibitory molecules and further the field was replete with prior art demonstrating predictable results of increased stability and enhanced uptake of nucleic acid molecules. For example, Manoharan II summarizes the prior art and states "oligonucleotide conjugates have been evaluated in a wide range of cell culture and in vitro experiments" and "the value of conjugation chemistry has been clearly demonstrated by these studies" and states further that oligonucleotide conjugates improve the pharmacokinetic properties of the oligonucleotide, such as binding affinity for the target and nuclease resistance such that one can synthesize an ideal drug with predictable results. It would have been a design choice and a matter of routine

experimentation to covalently attach the dendrimer to the 5' end of the complementary strand using any of the linkers as described above.

Therefore, because the claimed oligonucleotide conjugates were known in the art at the time of the invention of the instantly claimed invention and because such conjugates were known to efficiently improve the cellular delivery of oligonucleotides and increase their affinity for the target gene as well as increase their resistance to nucleases, it would have been obvious to one skilled in the art to use the conjugates taught by Manoharan et al. and Cook et al. to achieve the predictable result of improvement in cellular delivery of nucleic acid molecules.

Thus, the instantly claimed invention would have been obvious to one of skill in the art at the time the invention was made.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 103

The rejection of claims 86, 89, 90, 94-98, 100-102, 110-119 under 35 U.S.C. 103(a) as being unpatentable over Rana, T. (US 2005/0020521) in view of Florence et al. (Journal of Controlled Release, 2000, Vol. 65: 253-259), Manoharan, M. (20030064492, "Manoharan I") and Cook et al. (U.S. Patent No. 6,803,198) and evidenced by Manoharan, M. (Applicant's IDS 02/13/2006, "Manoharan II") is withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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/Kimberly Chong/
Primary Examiner
Art Unit 1635